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     (FILE 'HOME' ENTERED AT 18:35:42 ON 12 NOV 2003)

     FILE 'MEDLINE, BIOSIS, SCISEARCH, CANCERLIT, LIFESCI, CAPLUS, BIOTECHDS'
     ENTERED AT 18:36:10 ON 12 NOV 2003
L1          3170 S BQ788 OR (BQ(W)788) OR IRL1038 OR (IRL(W)1038) OR RES7011 OR
L2            19 S L1 AND MELANOMA
L3             9 DUP REM L2 (10 DUPLICATES REMOVED)

     FILE 'PCTFULL, USPATFULL, EUROPATFULL' ENTERED AT 18:42:42 ON 12 NOV 2003
L4            69 S BQ788 OR (BQ(W)788) OR IRL1038 OR (IRL(W)1038) OR RES7011 OR
L5             6 S L4 AND MELANOMA
L6           130 S ENDOTHELIN(W)B(W)REC?
L7         52588 S ETB OR ET(W)B
L8           968 S ETH(W)1
L9            52 S ETH1
L10        53542 S L7 OR L8 OR L9
L11           82 S L10(5A)ANTAGONIST#
L12            6 S L11 AND MELANOMA#

     FILE 'MEDLINE, BIOSIS, SCISEARCH, CANCERLIT, LIFESCI, CAPLUS, BIOTECHDS'
     ENTERED AT 18:54:47 ON 12 NOV 2003
L13        12242 S ETB OR (ET(W)B) OR ETH1 OR (ETH(W)1)
L14         7043 S L13 AND ANTAGONIST?
L15           14 S L14 AND MELANOMA#
L16            3 S L15 AND PY<2000
L17            3 DUP REM L16 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 18:59:55 ON 12 NOV 2003
                E IRL1038
                E IRL(W)1038
L18            1 S IRL(W)1038
L19            0 S IRL1038

     FILE 'CAPLUS' ENTERED AT 19:01:13 ON 12 NOV 2003
L20           17 S L18
L21            0 S L20 AND MELANOMA#

     FILE 'MEDLINE, BIOSIS, SCISEARCH, CANCERLIT, LIFESCI, CAPLUS, BIOTECHDS'
     ENTERED AT 19:05:29 ON 12 NOV 2003
L22          196 S CYS11(W)CYS15 OR C11(W)C15 OR (CYS?(W)11(2W)CYS?(W)15)
L23            0 S L22 AND MELANOMA#

     FILE 'PCTFULL, USPATFULL, EUROPATFULL' ENTERED AT 19:07:59 ON 12 NOV 2003
L24          565 S CYS11(W) CYS15 OR C11(W) C15 OR (CYS?(W) 11(2W) CYS?(W) 15)
L25            2 S L24 AND MELANOMA#
L26            0 S L10 AND L25

     FILE 'MEDLINE, BIOSIS, SCISEARCH, CANCERLIT, LIFESCI, CAPLUS, BIOTECHDS'
     ENTERED AT 19:51:40 ON 12 NOV 2003
L27          209 S L1 AND (CANCER? OR TUMOR? OR TUMOUR? OR MALIGNAN? OR NEOPLAS?
L28           67 S L27 AND PY<1999
L29           23 DUP REM L28 (44 DUPLICATES REMOVED)
L30          103 S ((ET(W)B)OR ETB OR ENDOTHELIN)(5A)(ANTISENSE OR (ANTI(W)SENSE
L31           44 S L30 AND PY<1999
L32           24 DUP REM L31 (20 DUPLICATES REMOVED)
L33         4404 S ENDOTHELIN(W)3
L34          102 S ANTAGONI?(5A)L33
L35            8 S L34 AND (CANCER? OR TUMOR? OR TUMOUR? OR MALIGNAN? OR NEOPLA
L36            4 DUP REM L35 (4 DUPLICATES REMOVED)
```

L5 ANSWER 6 OF 6 USPATFULL on STN
ACCESSION NUMBER: 2000:61727 USPATFULL
TITLE: Methods and compositions for treatment of cell proliferative disorders
INVENTOR(S): Vournakis, John N., Charleston, SC, United States
Finkielsztein, Sergio, Chestnut Hill, MA, United States
Pariser, Ernest R., Belmont, MA, United States
PATENT ASSIGNEE(S): Marine Polymer Technologies, Inc., Danvers, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6063911		20000516
APPLICATION INFO.:	US 1998-218288		19981222 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-471290, filed on 6 Jun 1995, now patented, Pat. No. US 5858350 which is a continuation-in-part of Ser. No. US 1994-347911, filed on 1 Dec 1994, now patented, Pat. No. US 5623064 which is a continuation-in-part of Ser. No. US 1993-160569, filed on 1 Dec 1993, now patented, Pat. No. US 5622834
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lankford, Jr., Leon B.
ASSISTANT EXAMINER: Tate, Christopher R.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 12 Drawing Page(s)
LINE COUNT: 2018
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of the few tumors to express ETB receptors that have a similar affinity for all three isoforms of endothelin is **melanoma** (Yohn et al., 1994, Biochem. Biophys. Res. Comm. 201 (1): 449-457). Interestingly, ETB receptors are highly expressed in primary or. . .

DRWD FIG. 7. Endothelin receptor antagonist Ro61 inhibition of B16 **melanoma** cell proliferation in vitro. Ro61 was added at increasing concentrations to a 96 well culture plate to which B16 cells. . .

DRWD FIG. 8. ETA and ETB agonists reversal of Ro61 inhibition of B16 **melanoma** cell proliferation in vitro. B16 cells were cultured with either, BQ-3020-[Ac-[Ala11,Ala15]-endothelin(6,21), an ETA agonist (closed triangle), [Ala.sup.1,3,11,15]-endothelin1, an ETB. . .

DRWD FIG. 10. Ro61 inhibition of B16 **melanoma** intraperitoneal metastases in vivo. C57BL/6 mice were injected intraperitoneally with B16 cells and one day later, the mice were injected. . .

DRWD FIG. 11. Long term survival of Ro61-treated C57BL/6 mice after intraperitoneal B16 **melanoma** challenge. C57BL/6 mice were injected intraperitoneally with B16 cells. Animals were randomly separated into 4 groups for either of the. . .

DETD . . . peptide-based endothelin receptor antagonists useful in the compositions and methods of the invention include BQ-123 (Cyclo(-D-Trp-D-Asp-L-Pro-D-Val-L-Leu-), BQ-153, BQ-238, BQ-485, BQ-610, **BQ-788**, BQ-928, TAK-044, FR139317 (Perhydroazepin-1-ylcarbonyl-L-leucyl-(1-methyl)-D-tryptophyl-[3-(2-pyridyl)]-D-alanine), **RES-701-1**, PD 142893 (Acetyl-(3,3-diphenyl-D-alanine)-L-Leu-L-Asp-L-Ile-L-Ile-L-Trp), PD 145065, CP 170687, Ac-DBhg16-Leu-Asp-Ile and ET-1[Dprl-Asp 15].

DETD Ro61 Inhibition of **Melanoma** Cell Proliferation in vitro

DETD . . . cells were evaluated for use as an endothelin responsive tumor model system. The B16 cells, i.e., from the B16 murine **melanoma** cell line (of fibroblastic origin), were obtained from the American Type

Culture Collection (Rockville Md.) as a frozen stock. The. . .

DETD The inhibitory effect of Ro61 on the B16 **melanoma** cells is depicted in FIG. 7. Proliferation of Ro61-treated cells is expressed as a percentage of untreated control cells. Mean. . .

DETD Ro61 Induction of B16 **Melanoma** Tumor Apoptotic Cell Death

DETD As depicted in FIG. 9, the endothelin antagonist Ro61 induced apoptosis in B16 **melanoma** cells in culture. For example, the addition of 1 .mu.M of Ro61 to the B16 cells led to an increase. . .

DETD Inhibition of B16 **Melanoma** Intraperitoneal Metastases in vivo by an Endothelin Antagonist or an EA/p-GlcNAc Composition of the Invention

DETD . . . further studies to evaluate the impact of ETR antagonism on in vivo tumor growth utilizing an agressive intraperitoneal (IP) B16 **melanoma** metastases model. Thus, female C57BL/6 mice were injected intraperitoneally with 5.times.10.sup.4 B16 cells in 100 ml HBSS. One day later,. . .

DETD Long Term Survival of C57BL/6 Mice after Intraperitoneal B16 **Melanoma** Challenge with an Endothelin antagonist Alone or an EA/p-GlcNAc Composition of the Invention

DETD It is of interest to note that the B16 **melanoma** is an extremely virulent tumor, which results in a 0% survival rate consistently within 19-20 days of tumor injection. As. . .

DETD . . . show direct evidence that inhibiting the binding of endothelins to their receptors can affect the normal proliferation of a murine **melanoma** cell line, both in vitro and in vivo. The endothelin antagonist, Ro61, is an inhibitor of both the ETA and ETB receptors with an approximately 10-fold higher affinity for ETA. This correlates well with the dose dependent inhibition of **melanoma** cell proliferation by Ro61 in our experiments, as well as the stronger countering effect to this inhibition obtained by addition. . .

DETD It is also interesting to note that **melanoma** cells have been shown to express high levels of ET receptors and are more susceptible to endothelin antagonist, e.g., Ro61,. . .

L3 ANSWER 7 OF 9 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1998:104946 SCISEARCH
THE GENUINE ARTICLE: YT856
TITLE: Endothelin-B receptor-mediated Ca2+ signaling in human melanocytes
AUTHOR: Kang H Y; Kang W H; Lee C O (Reprint)
CORPORATE SOURCE: POHANG UNIV SCI & TECHNOL, DEPT LIFE SCI, POHANG 790784, SOUTH KOREA (Reprint); POHANG UNIV SCI & TECHNOL, DEPT LIFE SCI, POHANG 790784, SOUTH KOREA; AJOU UNIV, SCH MED, DEPT DERMATOL, SUWON 442749, SOUTH KOREA
COUNTRY OF AUTHOR: SOUTH KOREA
SOURCE: PFLUGERS ARCHIV-EUROPEAN JOURNAL OF PHYSIOLOGY, (FEB 1998) Vol. 435, No. 3, pp. 350-356.
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
ISSN: 0031-6768.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 27

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The mechanism of an endothelin-1-(ET-1-) induced intracellular Ca2+ ([Ca2+](i)) increase and the receptor subtype(s) responsible for this effect in single human melanocytes were studied using fura-2/AM. ET-1 induced a transient increase in [Ca2+](i) in a concentration-dependent manner, The transient [Ca2+](i) increase was followed by a sustained plateau level of [Ca2+](i) which was higher than the initial [Ca2+](i) level, IRL-1620, a specific ET-B receptor agonist, increased [Ca2+](i) in a dose-dependent manner, **BQ-788**, a specific ET-B receptor antagonist, abolished the ET-1-induced [Ca2+](i) increase. but BQ-123, a specific ET-A receptor antagonist, failed to prevent it. U73122, an inhibitor of phospholipase C (PLC), inhibited the ET-1-induced [Ca2+](i) rise in a dose-dependent manner, Prior depletion of intracellular Ca2+ stores with thapsigargin, an inhibitor of Ca2+-ATPase of the endoplasmic reticulum, abolished the ET-1-induced Ca2+ transient, whereas removal of extracellular Ca2+ with EGTA eliminated the sustained rise. These results suggest that in cultured human melanocytes the binding of ET-1 to ET-B receptors and the subsequent activation of PLC mediate ET-1-induced [Ca2+](i) increase, The transient [Ca2+](i) increase is attributed to mobilization of Ca2+ from inositol 1,4,5-trisphosphate-sensitive intracellular Ca2+ stores, and the sustained [Ca2+](i) level may be related to the influx of extracellular Ca2+.

L3 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 96216721 MEDLINE
DOCUMENT NUMBER: 96216721 PubMed ID: 8645250
TITLE: Decreased ET(B) receptor expression in human metastatic **melanoma** cells.
AUTHOR: Kikuchi K; Nakagawa H; Kadono T; Etoh T; Byers H R; Mihm M C; Tamaki K
CORPORATE SOURCE: Department of Dermatology, Tokyo University Branch Hospital, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Feb 27) 219 (3) 734-9.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 19970203
Entered Medline: 19960715

AB In this study, we examined the endothelin (ET) receptor subtype involved in mitogenic signaling in human primary and metastatic **melanoma** cell lines. In a reverse transcriptase-polymerase chain reaction (RT-PCR) study, ET(B) mRNA expression in metastatic **melanoma** cells was decreased from that of primary **melanoma**. Only RPM-EP, a primary recurrent **melanoma** cell line, showed strong ET(A) mRNA expression. ET-1 and ET-3 stimulated DNA synthesis of primary and recurrent cutaneous **melanoma** cells in serum-deprived cultures. The growth response to ET-1 in metastatic **melanoma** cells was decreased from that in primary **melanoma** cells. [125I]-IRL-1620 binding to PM-WK, a primary **melanoma** cell line, was significantly blocked by excessive amounts of unlabeled **BQ-788**. [125I]-IRL-1620 binding to metastatic **melanoma** cells was significantly decreased from that of primary **melanoma** cells. From these results, we conclude that the mitogenic effects of ET in human primary **melanoma** are mainly mediated through ET(B) receptors and that down-regulation of ET(B) receptors causes the decreased growth response of ET-1 in metastatic **melanoma** cells.

L3 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:598188 CAPLUS
DOCUMENT NUMBER: 125:244458
TITLE: Decrease in ETB receptor in cultured human metastatic **melanoma** cells
AUTHOR(S): Kikuchi, Kanako; Kadono, Takafumi; Etoh, Takafumi; Nakagawa, Hidemi; Tamaki, Kunihiko
CORPORATE SOURCE: Branch Hospital, Tokyo University, Tokyo, 112, Japan
SOURCE: International Congress Series (1996), 1096(Melanogenesis and Malignant Melanoma: Biochemistry, Cell Biology, Molecular Biology, Pathophysiology, Diagnosis and Treatment), 77-85
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, the authors examd. the endothelin (ET) receptor subtype involved in mitogenic signaling in human primary and metastatic **melanoma**. In a reverse transcriptase-polymerase chain reaction (RT-PCR) study, ETB mRNA expression in metastatic **melanoma** cells was decreased compared to primary **melanoma**. Only RPM-EP, a primary recurrent **melanoma** cell line, showed strong ETA mRNA expression. ET-1 and ET-3 stimulated DNA synthesis of primary and recurrent cutaneous **melanoma** cells in serum-deprived cultures. The growth response to ET-1 in metastatic **melanoma** cells was decreased compared to primary **melanoma** cells. [125I]-IRL-1620 binding to PM-WK, a primary **melanoma** cell line, was significantly blocked by excessive amts. of unlabeled **BQ-788**. [125I]-IRL-1620 binding to metastatic **melanoma** cells was significantly decreased compared to primary **melanoma** cells. From these results, the authors conclude that the mitogenic effects of ET in human primary **melanoma** are mainly mediated through ETB receptors and that down-regulation of ETB receptors causes the decreased growth response of ET-1 in metastatic **melanoma** cells.

L32 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:30282 CAPLUS
DOCUMENT NUMBER: 130:206316
TITLE: The possible role of sense and antisense peptide interactions in the generation and maintenance of the tertiary structure of a protein
AUTHOR(S): Okada, Hidechika
CORPORATE SOURCE: Department of Molecular Biology, Nagoya City University School of Medicine, Nagoya, 467-8601, Japan
SOURCE: Anticancer Research (1998), 18(5D), 3927-3930
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: Anticancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with .apprx.4 refs. Antisense peptide is an amino acid sequence translated from antisense sequence of mRNA for a peptide sequence (sense peptide). Previous evidence indicates that sense and antisense peptides have a tendency to interact with each other. We expected that this kind of interaction might be involved in the formation and maintenance of tertiary structure of protein mols. Many amino acids have several RNA codons and we regarded amino acids coded by anti-codons of all of codons of each amino acid as antisense amino acids. On this stand point, we generated a computer program to search for antisense peptides. Then we found that there are peptide sequences which are antisense to several peptide sequences in a protein mol., and these peptide sequences have been termed as antisense homol. boxes (AHB). AHB peptides were synthesized and some of them had a potent capacity to interfere with the function of the mol.

L29 ANSWER 5 OF 23 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1998156612 MEDLINE
DOCUMENT NUMBER: 98156612 PubMed ID: 9496898
TITLE: Endothelin-1 production and agonist activities in cultured prostate-derived cells: implications for regulation of endothelin bioactivity and bioavailability in prostatic hyperplasia.
AUTHOR: Walden P D; Ittmann M; Monaco M E; Lepor H
CORPORATE SOURCE: Department of Urology, NYU Medical Center, New York 10016, USA.. paul.walden@nyu.edu
SOURCE: PROSTATE, **(1998 Mar 1)** 34 (4) 241-50.
Journal code: 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980407
Last Updated on STN: 20000303
Entered Medline: 19980320

AB BACKGROUND: Endothelin-1 (ET-1) interacts with specific G-protein-coupled receptors to initiate short-term (contraction) and long-term (mitogenesis) events in target cells. ET-1 is an abundant prostate secretory protein that, in its biologically active form, elicits prostatic smooth muscle contraction. The present study was designed to determine the effects of ET-1 on prostate cell growth and to examine the regulation of endogenous ET-1 activity and bioavailability. METHODS: Primary cultures of prostate secretory epithelial (PE) and prostate fibromuscular stromal (PS) cells were established from benign human prostate tissue. RESULTS: In culture, PE cells secrete immunoreactive ET-1 (38.5 +/- 1.6 pg/ml/10(6) cells/24 hr) into the conditioned medium. Levels of immunoreactive ET-1 produced by PS cells were more than 10-fold lower. Endothelin-converting enzyme-1 (ECE-1) mRNA was detected in PE cells and not in PS cells; however, big ET-1 was the predominant immunoreactive ET-1 secretory product of PE cells. The ET(B) endothelin receptor was the predominant subtype in both PE and PS cells. In PS cells, but not PE cells, ET-1 induced significant inositol phosphate accumulation and [3H]-thymidine uptake. Agonist activity was inhibited by the ET(B) receptor selective antagonist, **BQ 788**. Intact PE cell monolayers secrete ET-1 through the apical surface, consistent with secretion of ET-1 into the glandular lumen in vivo. CONCLUSIONS: On the basis of these findings, regulation of ET-1 activity and bioavailability appears to be tightly regulated. Such findings have important implications in the pathophysiology of prostate disease.

L29 ANSWER 6 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1998:325861 BIOSIS
DOCUMENT NUMBER: PREV199800325861
TITLE: Mitogenic activity of endothelin on human cultured prostatic smooth muscle cells.
AUTHOR(S): Saita, Yuji [Reprint author]; Yazawa, Hidenori; Koizumi, Tomonobu; Morita, Takashi; Tamura, Toshinari; Takenaka, Toichi; Honda, Kazuo
CORPORATE SOURCE: Inst. Drug Discovery Res., Yamanouchi Pharm., 21 Miyukigaoka, Tsukuba, Ibaraki 305, Japan
SOURCE: European Journal of Pharmacology, (May 15, 1998) Vol. 349, No. 1, pp. 123-128. print.
CODEN: EJPHAZ. ISSN: 0014-2999.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Jul 1998
Last Updated on STN: 22 Jul 1998

AB The effects of endothelins on human prostatic smooth-muscle cell growth were examined. Endothelin-1 and endothelin-3 induced a concentration-dependent increase in DNA synthesis and also promoted cell growth. Use of subtype selective antagonists BQ-123 ((cyclo(D-Trp-D-Asp(ONa)-Pro-D-Val-Leu); endothelin ETA receptor selective) and **BQ -788** ((N-cis-2,6-dimethylpiperidinocarbonyl-L-gamma-methyl LeU-D-Trp-(COOMe)-D-Nle-ONa); endothelin ETB receptor selective), indicated that mitogenic effects of endothelin were mediated through activation of both endothelin ETA and ETB receptors. The mitogenic effects of endothelin-1 and endothelin-3 were significantly inhibited by pretreatment of the cells with pertussis toxin. However, mitogenesis due to basic fibroblast growth factor was not affected. In conclusion, endothelin has mitogenic effects on human prostatic smooth muscle cells through activation of both endothelin ETA and ETB receptors via different signalling pathways from basic fibroblast growth factor. This may contribute to smooth muscle hyperplasia associated with benign prostatic hyperplasia.

L29 ANSWER 12 OF 23 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 97419945 MEDLINE
DOCUMENT NUMBER: 97419945 PubMed ID: 9274451
TITLE: Endothelin expression and responsiveness in human ovarian **carcinoma** cell lines.
AUTHOR: Moraitis S; Langdon S P; Miller W R
CORPORATE SOURCE: Imperial Cancer Research Fund Medical Oncology Unit, Western General Hospital, Edinburgh, U.K.
SOURCE: EUROPEAN JOURNAL OF CANCER, **(1997 Apr)** 33 (4) 661-8.
Journal code: 9005373. ISSN: 0959-8049.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970922
Last Updated on STN: 19970922
Entered Medline: 19970909

AB To elucidate the potential role of endothelins (ETs) as growth regulators in ovarian **carcinoma** cells in culture, expression of endothelins and their receptors were measured in two ovarian **cancer** cell lines (PEO4 and PEO14), together with the effect of the exogenous addition of endothelins on the growth of these cell lines in vitro. RT-PCR analysis of mRNA prepared from PEO4 and PEO14 indicated the presence of ET-1 and ET-3 mRNA. Immunoreactive ET-1-like peptide was found in media from cultures of both PEO4 (1.7 +/- 0.4 fmol/10(6) cells/72 h) and PEO14 (20.2 +/- 6.8 fmol/10(6) cells/72 h) cell lines. Radioligand binding studies using 125I-ET-1 and membrane fractions were consistent with PEO4 cells having two receptor sites of either high affinity (Kd = 0.065 nM, Bmax = 0.047 pmol/mg protein) or lower affinity sites (Kd = 0.49 nM, Bmax = 0.23 pmol/mg protein). Studies using membrane fractions of PEO14 cells indicated that this cell line has only a single lower affinity binding site (Kd = 0.56 nM, Bmax = 0.31 pmol/mg protein). However, RT-PCR analysis indicated the presence of mRNA from both ETA and ETB receptors in PEO4 and PEO14 cell lines. Exogenous addition of ETs to PEO4 and PEO14 cells at concentrations of 10(-10)-10(-7)M resulted in specific dose-dependent increases in cell number for ET-1 (with maximum effects at 10(-10) and 10(-9)M for PEO4 and PEO14, respectively) and ET-2 (maximum effects at 10(-8) and 10(-9)M for PEO4 and PEO14, respectively) but not for ET-3. Experiments on the growth of PEO14 cells using BQ123 (ETA-R) antagonist and "antisense" oligonucleotide against the ETA-R, in the absence of exogenous ETs, suggested that immunoreactive ET-1-like material secreted by PEO14 cells can affect their growth in an autocrine manner. These results would be consistent with ET-1 acting as a possible autocrine growth regulator in human ovarian **carcinoma** cells.

L29 ANSWER 14 OF 23 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 97474432 MEDLINE
DOCUMENT NUMBER: 97474432 PubMed ID: 9335456
TITLE: Vascular response of **tumour** and normal tissues to endothelin-1 following antagonism of ET(A) and ET(B) receptors in anaesthetised rats.
AUTHOR: Bell K M; Prise V E; Chaplin D J; Wordsworth S; Tozer G M
CORPORATE SOURCE: Tumour Microcirculation Group, Mount Vernon Hospital, Northwood, UK.. bell@graylab.ac.uk
SOURCE: INTERNATIONAL JOURNAL OF CANCER, **(1997 Oct 9)** 73 (2) 283-9.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971029

AB Modification of blood flow by endothelin-1 (ET-1) was examined in the s.c. HSN fibrosarcoma and compared to normal tissues of anaesthetised CBH/CBi rats. The ET receptor subtypes involved in the response were investigated using the ET(A) and ET(B) receptor antagonists BQ-610 and **BQ-788**, respectively. Blood flow and vascular resistance were determined using the uptake of radiolabelled iodo-antipyrine (125I-IAP). BQ-610 or **BQ-788** was infused for 30 min prior to blood flow determination. ET-1 was administered 15 min into the infusion time. BQ-610 and **BQ-788** infused alone did not modify any vascular parameters. **Tumour** blood flow increased slightly following ET-1, contrasting with most normal tissues, in which blood flow was reduced. Vascular resistance increased in all tissues, including the **tumour**. Neither antagonist significantly modified the ET-1-induced changes in **tumour** blood flow or vascular resistance, whereas in the majority of normal tissues BQ-610 attenuated and **BQ-788** potentiated the vascular resonse to ET-1. Our results show that the HSN **tumour** vasculature is only weakly responsive to ET- 1 and antagonism of its effects by BQ-610 and **BQ -788**. This contrasts with the majority of normal tissues, in which ET- 1 induces an intense vasoconstriction.

L29 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:7997 CAPLUS
DOCUMENT NUMBER: 126:99778
TITLE: ICAM-1 expression on cardiac myocytes and aortic endothelial cells via their specific endothelin receptor subtype
AUTHOR(S): Hayasaki, Yoko; Nakajima, Masatoshi; Kitano, Yoshinori; Iwasaki, Takanori; Shimamura, Toshitake; Iwaki, Kazumi
CORPORATE SOURCE: Discovery Res. Lab. II, Shionogi & Co., Ltd., Toyonaka, 561, Japan
SOURCE: Biochemical and Biophysical Research Communications (1996), 229(3), 817-824
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Endothelin-1 (ET-1) and endothelin-3 (ET-3) increased the expression of intercellular adhesion mol.-1 (ICAM-1) on rat neonatal cultured cardiac myocytes and rat aortic endothelial cells. ET-1-induced ICAM-1 expression on cardiac myocytes was inhibited by a selective ETA receptor antagonist, S-0139, but not by a selective ETB receptor antagonist, **BQ788**. ET-3-induced ICAM-1 expression on endothelial cells was inhibited by **BQ788** but not by S-0139. Protein kinase C (PKC) inhibitor staurosporine inhibited ETs-induced ICAM-1 expression on both cell types. Treatment of the cells with ETs increased neutrophil adhesion, which was inhibited by S-0139 and staurosporine on cardiac myocytes and by **BQ788** and staurosporine on endothelial cells. These results suggest that ETs induce neutrophil adhesion to cardiac myocytes and aortic endothelial cells by increasing ICAM-1 expression, which mediate via ETA receptor on cardiac myocytes and via ETB receptor on aortic endothelial cells. ICAM-1 expression induced by activation of ETA and ETB receptors appears to be mediated through the PKC pathway.

L32 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:782003 CAPLUS
DOCUMENT NUMBER: 123:188598
TITLE: Endothelin-converting enzyme, sequences of cattle and human enzyme cDNAs, and their pharmacological uses
INVENTOR(S): Kroeger, Burkhard; Seulberger, Harald; Meyer, Thomas; Schmidt, Martin; Jacob, Elard; Otter, Rainer; Subkowski, Thomas; Hillen, Heinz
PATENT ASSIGNEE(S): BASF A.-G., Germany
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9514095	A1	19950526	WO 1994-EP3706	19941110	<--
W: AU, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, NO, NZ, PL, RU, SK, UA, US					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
DE 4339100	A1	19950518	DE 1993-4339100	19931116	<--
DE 4403665	A1	19950810	DE 1994-4403665	19940207	<--
DE 4412372	A1	19951019	DE 1994-4412372	19940412	<--
AU 9481070	A1	19950606	AU 1994-81070	19941110	<--
EP 728209	A1	19960828	EP 1995-900130	19941110	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE					
JP 09505733	T2	19970610	JP 1994-514199	19941110	<--
BR 9408077	A	19970812	BR 1994-8077	19941110	<--
FI 9602047	A	19960712	FI 1996-2047	19960514	<--
NO 9602023	A	19960716	NO 1996-2023	19960515	<--
US 6066502	A	20000523	US 1996-646273	19960516	

PRIORITY APPLN. INFO.:

DE 1993-4339100	A	19931116	
DE 1994-4403665	A	19940207	
DE 1994-4412372	A	19940412	
WO 1994-EP3706	W	19941110	

AB The invention relates to endothelin-converting enzymes contg. the polypeptide sequence described or functional fragments thereof, genes which code for such enzymes, and processes for producing the said enzymes and use of the enzymes in pharmacol.

L29 ANSWER 17 OF 23 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 96223664 MEDLINE
DOCUMENT NUMBER: 96223664 PubMed ID: 8630991
TITLE: Endothelin-1 production and decreased endothelin B receptor expression in advanced prostate **cancer**.
AUTHOR: Nelson J B; Chan-Tack K; Hedican S P; Magnuson S R; Opgenorth T J; Bova G S; Simons J W
CORPORATE SOURCE: James Buchanan Brady Urological Institute Research Laboratories, Johns Hopkins Hospital, Baltimore, Maryland 21287-2411, USA.
CONTRACT NUMBER: CA-58236 (NCI)
SOURCE: CANCER RESEARCH, **(1996 Feb 15)** 56 (4) 663-8.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960715
Last Updated on STN: 20000303
Entered Medline: 19960703

AB The potent vasoconstrictor endothelin-1 (ET-1) is at its highest concentration in the normal human ejaculate and is associated with the progression of metastatic prostate **cancer**. ET-1 protein expression is detected in situ in 14 of 14 primary **cancers** and 14 of 16 metastatic sites of human prostatic **carcinoma**. Exogenous ET-1 induces prostate **cancer** proliferation directly and enhances the mitogenic effects of insulin-like growth factor I, insulin-like growth factor II, platelet-derived growth factor, basic fibroblast growth factor, and epidermal growth factor in serum-free conditions in vitro. The ETA-selective receptor antagonist A-127722 inhibits ET-1-stimulated growth, but the ETB-selective receptor antagonist **BQ-788** does not. ET-3, an ETB-selective agonist, also had no effect on prostate **cancer** growth. No specific ETB-binding sites could be demonstrated in any established human prostate **cancer** cell line tested, and ETB mRNA, detected by reverse transcription PCR, was reduced. The predominance of ETB binding on human benign prostatic epithelial tissue is not present in metastatic prostate **cancer** by autoradiography. In human prostate **cancer** progression to metastases, ET-1 and ETA expression are retained, whereas ETB receptor expression is reduced.

L32 ANSWER 18 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 4

ACCESSION NUMBER: 1995:203063 BIOSIS
DOCUMENT NUMBER: PREV199598217363
TITLE: Endothelin ET-A and ET-B mRNA and receptors expressed by smooth muscle in the human vasculature: Majority of the ET-A sub-type.
AUTHOR(S): Davenport, Anthony P. [Reprint author]; O'Reilly, Gillian; Kuc, Rhoda E.
CORPORATE SOURCE: Clin. Pharmacol. Unit, Univ. Cambridge, Addenbrooke's Hosp., Cambridge CB2 2QQ, UK
SOURCE: British Journal of Pharmacology, (1995) Vol. 114, No. 6, pp. 1110-1116.
CODEN: BJPCBM. ISSN: 0007-1188.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 1995
Last Updated on STN: 23 May 1995

AB 1. We measured the ratio of ET-A and ET-B sub-types in the media (containing mainly smooth muscle) of human cardiac arteries (aorta, pulmonary and coronary), internal mammary arteries and saphenous veins. 2. In saturation experiments, (125I)-endothelin-1 ((125I)-ET-1) bound with high affinity to the media of each vessel (n = 3 individuals or homogenate preparations +- s.e.mean): coronary artery, K-D = 0.14+-0.02 nM, B-max = 71.0 +- 21.0 fmol mg-1 protein; pulmonary artery, K-D=0.85 +- 0.25 nM, B-max = 15.2 +- 10.3 fmol mg-1 protein; aorta, K-D = 0.51 +- 0.02 nM, B-max = 9.4 +- 4.4 fmol mg-1 protein; internal mammary artery, K-D = 0.34 +- 0.31 nM, B-max = 2.0 +- 0.5 fmol mg-1 protein and saphenous vein, K-D = 0.28 +- 0.05 nM, B-max = 52.8 +- 1.0 fmol mg-1 protein. In each vessel, over the concentration-range tested, Hill slopes were close to unity and a one site fit was preferred to a two site model. 3. In competition binding assays, the ET-A selective ligand, BQ123 inhibited the binding of 0.1 nM (125I)-ET-1 to the media in a biphasic manner. In each case, a two site fit was preferred to a one or three site model: coronary artery, K-DET-A = 0.85 +- 0.03 nM, K-DET-B = 7.58 +- 2.27 mu-M, ratio = 89: 11%; pulmonary artery, K-DET-A = 0.27 +- 0.05 nM, K-DET-B = 24.60 +- 5.34 mu-M, ratio = 92:8%; aorta, K-DET-A = 0.80 +- 0.40 nM, K-DET-B = 2.67 +- 2.60 mu-M ratio = 89:11%; saphenous vein, K-DET-A = 0.55 +- 0.17 nM, K-DET-B = 14.4 +- 0.26 mu-M, 85:15% (n = 3 individuals or homogenate preparations +- s.e.mean). BQ123 showed up to 18000 fold selectivity for the ET-A over the ET-B sub-type. The ET-A-selective ligand, (125I)-PD151242 labelled 85% of the receptors detected by a fixed concentration of (125I)-ET-1 in media of internal mammary artery, measured by quantitative autoradiography. In contrast, the density of ET-B receptors detected with (125I)-BQ3020 was 7.0 +- 1.5 amol mm-2, representing about 8% of (125I)-ET-1. 4. A single band corresponding to the expected position for mRNA encoding the ET-A receptor (299 base pairs) was found in the media in each of the five vessels (n = 3 individuals) using reverse-transcriptase polymerase chain reaction assays. A single band corresponding to the ET-B sub-type (428 base pairs) was also always detected. 5. 35S-labelled **antisense** probes to ET-A and **ET-B** hybridised to the media of epicardial coronary arteries as well as intramyocardial vessels, confirming the presence of mRNA encoding both sub-types in the vascular smooth muscle of the vessel wall. 6. Although mRNA for both receptors was detected, competition binding using BQ123 demonstrated that the majority (at least 85%) of ET receptors present in smooth muscle are the ET-A sub-type. These results provide further support for the hypothesis that the ET-A sub-type is the receptor that must be blocked in humans to produce a beneficial vasodilatation in pathophysiological conditions where there is an increase in peptide concentration or receptor density.

L29 ANSWER 20 OF 23 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 95341539 MEDLINE
DOCUMENT NUMBER: 95341539 PubMed ID: 7616437
TITLE: Endothelin receptor in human astrocytoma U373MG cells: binding, dissociation, receptor internalization.
AUTHOR: Wu-Wong J R; Chiou W J; Magnuson S R; Opgenorth T J
CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Illinois, USA.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, **(1995 Jul)** 274 (1) 499-507.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950905
Last Updated on STN: 19970203
Entered Medline: 19950818

AB Endothelin (ET) receptor in human astrocytoma U373MG cells was characterized. ET-1, ET-3, sarafotoxin S6C, IRL1620, **BQ788**, Ro46-2005 and PD142893 inhibited specific [125I]ET-1 binding with Ki values of 0.03 0.06, 0.74, 5.01, 4.45, 2275 and 157 nM, respectively. ETA selective antagonists BQ123 and FR139317 at 1 microM did not block [125I]ET-1 binding. Reverse transcription-polymerase chain reaction confirmed the results from competition studies that U373 cells expressed predominantly ETB receptor. The Bmax and KD values of [125I]ET-1 binding were 0.15 pmol/1 x 10(6) cells and 0.23 nM. The molecular mass for the receptor was 45 kDa. ET-1 binding did not stimulate Ca+2 mobilization, phosphatidylinositol hydrolysis or arachidonic acid release, nor did it affect the intracellular cAMP or cGMP level. Interestingly, a majority of ET (> 80%) bound to the receptor was rapidly internalized, consistent with emerging evidence that a major function of ETB receptor is to clear ET. [125I]ET-1 binding was time-dependent and bound [125I]ET-1 was difficult to dissociate. In contrast, bound antagonists were much easier to dissociate. The results suggest that agonists and antagonists of the ET receptor exhibited different dissociation characteristics, with antagonist binding more reversible than agonist binding.

L29 ANSWER 21 OF 23 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 95385816 MEDLINE
DOCUMENT NUMBER: 95385816 PubMed ID: 7656997
TITLE: A new endothelin C-terminal analogue IBDP 064 antagonizes endothelin-3-induced cell proliferation.
AUTHOR: Sedo A; Pegoraro S; Rovero P; Revoltella R P
CORPORATE SOURCE: 1st Department of Medical Chemistry and Biochemistry, 1st Medical Faculty, Charles University, Praha, Czech Republic.
SOURCE: FOLIA BIOLOGICA, **(1995)** 41 (2) 97-105.
Journal code: 0234640. ISSN: 0015-5500.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951013
Last Updated on STN: 19970203
Entered Medline: 19951002

AB A series of C-terminal linear endothelin analogues were prepared and their activities in C6 rat glioma cell line were tested. Among the synthetic analogues, IBDP 064, Fmoc-Leu-Asp-Ile-Ile-Trp-OH, was the most potent and selective inhibitor of endothelin-3-induced cell proliferation. Its action was comparable with that of the previously described peptide **IRL 1038**, [Cys11-Cys15]-ET-1(11-21), an ETB specific inhibitor.

L32 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:182139 CAPLUS
DOCUMENT NUMBER: 120:182139
TITLE: Endothelins: a new target for pharmacological intervention?
AUTHOR(S): Benatti, L.; Fabbrini, M. S.; Vitale, A.
CORPORATE SOURCE: Biotechnol. Dep., Farmitalia Carlo Erba, Nerviano, Italy
SOURCE: Chimica Oggi (**1993**), 11(10), 19-24
CODEN: CHOGDS; ISSN: 0392-839X
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 78 refs. discussing the structure of endothelins, the question of whether a sp. **endothelin**-converting enzyme exists, **antisense** peptides, and **endothelin** receptor antagonists.

QP501.B43
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STIC-ILL

From: Canella, Karen
Sent: Wednesday, November 12, 2003 7:21 PM
To: STIC-ILL
Subject: ill order 09/305,084

Art Unit 1642 Location 8E12(mail)

Telephone Number 308-8362

Application Number 09/305,084

1. Biochemical and Biophysical research Communications, 1996 Feb 27, Vol. 219, No. 3, pp. 734-739

2. SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1998:104946 SCISEARCH
THE GENUINE ARTICLE: YT856
TITLE: Endothelin-B receptor-mediated Ca2+ signaling in human melanocytes
AUTHOR: Kang H Y; Kang W H; Lee C O (Reprint)
CORPORATE SOURCE: POHANG UNIV SCI & TECHNOL, DEPT LIFE SCI, POHANG 790784, SOUTH KOREA (Reprint); POHANG UNIV SCI & TECHNOL, DEPT LIFE SCI, POHANG 790784, SOUTH KOREA; AJOU UNIV, SCH MED, DEPT DERMATOL, SUWON 442749, SOUTH KOREA
COUNTRY OF AUTHOR: SOUTH KOREA
SOURCE: PFLUGERS ARCHIV-EUROPEAN JOURNAL OF PHYSIOLOGY, (FEB 1998) Vol. 435, No. 3, pp. 350-356.
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
ISSN: 0031-6768.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 27

RC261.A1 C2

From: Canella, Karen
Sent: Wednesday, November 12, 2003 8:46 PM
To: STIC-ILL
Subject: ill order 09/305,084

Art Unit 1642 Location 8E12(mail)

Telephone Number 308-8362

Application Number 09/305,084

1. Cancer Research, 1996 Feb 15, 56(4):663-668
2. Biochemical and Biophysical research Communications, 1996, Vol. 229, No. 3, pp. 817-824
3. International Journal of Cancer, 1997 Oct 9, 73(2):283-289
4. European Journal of Cancer, 1997 Apr, 33(4):661-668
5. Prostate, 1998 Mar 1, 34(4):241-250

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4. European Journal of Cancer, 1997 Apr, 33(4):661-668
5. Prostate, 1998 Mar 1, 34(4):241-250

STIC-ILL MPL RL261.A1I51

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RC261.H1E87

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